Attorney Docket No. 26581U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MARX et al. Examiner: JEAN-LOUIS, Samira

Serial No.: 10/524,821 Art Unit: 1617

Filed: February 18, 2005

For: **THE USE OF THE COMBINATION OF CICLESONIDE AND ANTIHISTAMINES FOR THE TREATMENT OF ALLERGIC RHINITIS**

Declaration Under 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Dr. Rolf Beume, declare and say:

1.1 That I am a citizen of the Federal Republic of Germany, residing at Bohlstr. 13, Konstanz 78465 (Germany).

1.2 That I have expert knowledge of the subject matter of the captioned application for U.S. Letters Patent.

1.3 That I have studied biology at the Ruhr-University Bochum, Germany and that I have a PhD graduation (Dr. rer. nat.)

1.4 That I have a graduation as "Specialist in Pharmacology" by the German Society of Experimental and Clinical Pharmacology and Toxicology (Fachpharmakologe DGPT)

1.5 That from 1981 – 1984, I was a Project leader for CNS and airway therapeutics at the department Product Development at Byk Gulden, Konstanz, Germany

1.6 That from 1984 – 1991, I was a Laboratory leader at the department Respiratory Pharmacology at Byk Gulden, Konstanz, Germany

1.7 That from 1991 – 1999, I was a Group leader at the department Respiratory Pharmacology at Byk Gulden, Konstanz, Germany

1.8 That from 1999 – 2006, I was the Head of the department Respiration and Inflammation Pharmacology at Byk Gulden/ALTANA Pharma, Konstanz, Germany

1.9 That I am currently working as Director at Respiratory Scientific Support at Nycomed, Konstanz, Germany.

2. Summary and Traversal of the 35 U.S.C. §103 rejections

2.1 I have intensively studied the Office Action dated September 30, 2009, as well as the cited prior art:
a) Magee et al., US Published Application 2002/0111495,
b) Calatayud et al., US Patent No. 5,482,934,
c) Szelenyl et al., PCT publication WO 01/022955, and
d) Schmidt et al., J. Clin. Pharmacology, 1999, Vol. 39, pp. 1062-9,
and I am aware that the examiner has rejected claims 1, 3-14 and 18-21 under 35 U.S.C. § 103(a) as being unpatentable over these references, either alone, or in various combinations.

2.2 Presently pending claim 1 is directed to a pharmaceutical composition for application to the mucosa comprising as active ingredients a combination of 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)phthalazinone (AZELASTINE), or a stereoisomer, a pharmaceutically acceptable salt or physiologically functional derivative thereof, and ciclesonide, or a pharmaceutically acceptable salt of ciclesonide, an epimer of ciclesonide, or a physiologically functional derivative of ciclesonide, and a pharmaceutically acceptable carrier and/or one or more excipients, wherein said pharmaceutical composition has an osmotic pressure of less than 290 mOsm.

2.3 The Examiner alleges in the rejections of claims 1, 3-14 and 18-21 under 35 U.S.C. § 103(a) that one of ordinary skill in the art would have found it obvious to arrive at the presently claimed subject matter from reading the disclosures contained in the cited references.

2.4 However, the subject matter as presently claimed in current claim 1 is clearly and unexpectedly superior, thereby rendering the presently claimed subject matter patentable over the cited references. In particular, the presently claimed "pharmaceutical composition for application to the mucosa comprising as active ingredients a combination of 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)phthalazinone (AZELASTINE), or a stereoisomer, a pharmaceutically acceptable salt or physiologically functional derivative thereof, and ciclesonide, or a pharmaceutically acceptable salt of ciclesonide, an epimer of ciclesonide, or a physiologically functional derivative of ciclesonide, and a pharmaceutically acceptable carrier and/or one or more excipients, wherein said pharmaceutical composition has an osmotic pressure of less than 290 mOsm" encompasses the combination product tested in the data presented herewith in Appendix A. The data presented herewith provides clear evidence that the presently claimed subject matter is unexpectedly superior for rapid onset and quick symptom relief (See page 2, paragraph 9 of the present application) for the combination product as presently claimed when compared to the technical effect of either agent alone.

2.5 It is clear from the data presented herein that the presently claimed combination of ciclesonide and azelastine is unexpectedly superior in reducing the occurrence of sneezes and nasal rubbings. The combination product yielded a much greater than additive effect when compared to each of the separate agents by themselves.

2.6 Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 3-14 and 18-21 under 35 U.S.C. § 103(a).

3. The undersigned Declarant declares further that all statements made herein and in the Appendix of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Signed at Konstanz 17. Feb, 2010

Beume

Dr. Rolf Beume

APPENDIX A

A combination product comprising ciclesonide and azelastine, and azelastine and ciclesonide alone were tested in an animal model for allergic rhinitis. The following results were obtained with respect to symptoms:

Animals

Male Balb/c mice were obtained by B&K Universal AB (Sollentuna, Sweden) and are 4-6 weeks old when the sensitisation began. They were allowed food and water ad libitum and kept in a room with a 12-hour light-dark cycle. 20 animals were included in each protocol group.

Sensitisation

Mice were sensitised to 10μg OVA grade III (Sigma chemical Co, St. Louis, MO, USA) and 4mg/ml Al $(OH)_3$ (Sigma Chemical Co) suspended in 0,2 ml PBS, given as an intraperitoneal injection (i.p.) on day 0, 7 and 14. The control group was not sensitised and received only 4mg/ml Al $(OH)_3$ suspended in 0,2 ml PBS i.p.

Treatment groups and readouts

The animals were randomly assigned to one of four groups. Treatment was performed on day 26-29 for all groups with intranasal instillation of the actual compound in hypotonic suspension, 25 μl into each nostril using a micropipette under slight anaesthesia with carbondioxide. Treatment was performed one hour before each challenge.

1. Hypotonic suspension (placebo), sick control group, n=20
2. Azelastine 5 μg as hypotonic suspension, n=20
3. Ciclesonide 3 μg as hypotonic suspension, n=20
4. Azelastine + Ciclesonide in the corresponding dosage dissolved in 25 μl hypotonic suspension, n=20
5. A comparison was performed with a non-sensitized group (normal control group) n=20

Readouts

Symptoms: Nasal rubbing and sneezes within 10 minutes after each challenge was tested.

Symptoms scores

The number of sneezes and nasal rubbings respectively where counted in five mice at the time and during the first 10 minutes after challenge. The number of sneezes or nasal rubbings respectively was expressed both for each individual time-point of challenge as well as compound scores for challenge 1 – 3 (sum of symptoms for all the challenges).

Results

The data sets for each parameter are illustrated in figure 1 and 2.

Symptoms

Number of sneezes/mouse during the first 10 minutes after challenge (compound score challenge 1-3) was significantly increased in allergic control group. The combination treatment of ciclesonide and azelastine showed significant reduction in sneezes (Fig. 1), whereas azelastine and ciclesonide alone had little or no effects, respectively. Individual numbers of sneezes/mouse at individual challenges 1, 2 and 3 displayed a similar pattern but were less pronounced at challenge 2 and 3 (data not shown).

During the first 10 minutes after first challenge, the number of nasal rubbings/mouse were significantly increased in allergic control group. All treatment groups displayed a significant reduction in number of rubbings/mouse with the combination of ciclesonide and azelastine displaying a superior effect for the combination (Fig. 2). Similarly as for sneezes, group pattern for rubbings at challenges 2 and 3 were similar but less pronounced (data not shown).

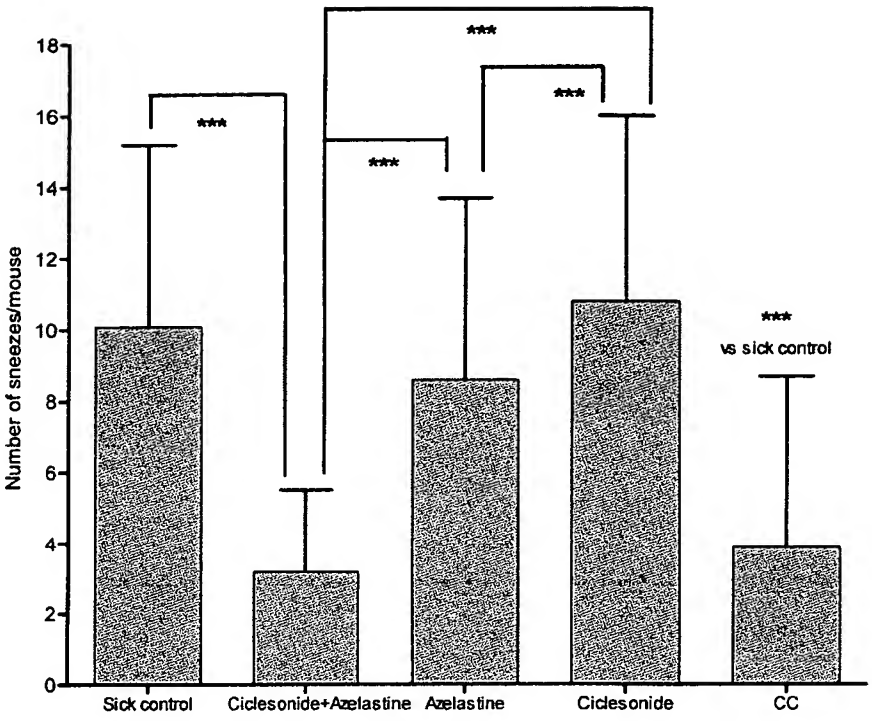

Figure 1. Number of sneezes per animal within 10 min after intranasal allergen challenge. Values represent cumulative data as the sum of symptoms for all the challenges. Values are given as arithmetric mean±SEM. Statistically significant changes are indicated with ***.

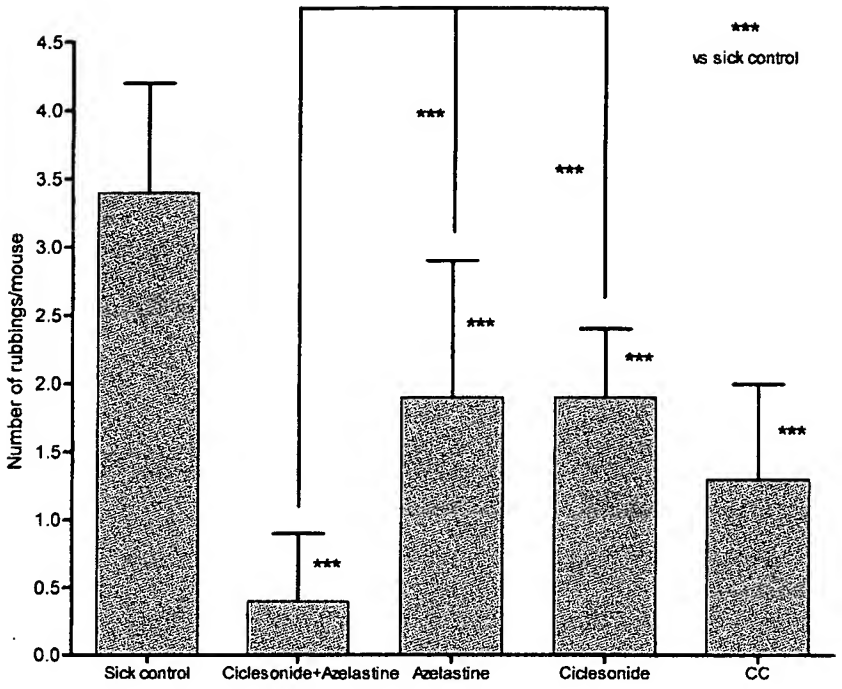

Figure 2: Number of nasal rubbings at challenge 1 within 10 min after intranasal allergen challenge. Values are given as arithmetic mean±SEM. Statistically significant changes are indicated with *** (significances within treatment groups as ***).

Abbreviations used within the text:

Ovalbumin	Ova
Sick Control	SC
Control – Control	CC